DRAFT Friday, June 20, 2003
Executive Summary

Second Annual Progress Report: Implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance* *Part 1: Domestic Issues*

Interagency Task Force on Antimicrobial Resistance

June 2003

INTRODUCTION

This is the second annual progress report on implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance (Part I Domestic Issues)* (1) which was released in January 2001 by the Federal Interagency Task Force on Antimicrobial Resistance. The plan provides a blueprint for federal actions to address the emerging threat of antimicrobial resistance (AR). The Task Force was formed in 1999, after hearings held by Senators Bill Frist (R - TN) and Edward Kennedy (D - MA), in recognition of the fact that addressing the multifaceted problem of AR required action by multiple agencies and departments. Co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), the Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), the Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (VA), the Environmental Protection Agency (EPA), and, since 2001, the US Agency for International Development (USAID).

The Action Plan was developed based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. Implementation is incremental, in collaboration with these and other partners, as resources become available. Part I of the Plan focuses on domestic issues; Part II, under development, will identify federal actions that more specifically address global AR issues in collaboration with the World Health Organization and other partners. The Task Force is continuing to meet to monitor implementation of the Plan and will release annual progress reports and seek additional input at public meetings.

This progress report contains an inventory of projects or activities that are being undertaken by the Task Force agencies to implement action items in the Plan. Like the Plan itself, this report is divided into four major sections: 1) surveillance, 2) prevention and control, 3) research, and 4) product development. The executive summary contains a brief overview of progress in implementing the top priority action items and the inventory of projects describes the status of activities for each action item. Projects applying to more than one action item in the same section are listed once and cross-referenced under the other action items in the section. Projects applying to action items in more than one section are repeated in each section.

Many projects listed in this progress report were initiated recently, after development of the Plan, and their outcome or impact cannot yet be assessed; however, such assessments are made when possible. Persons wishing more information about particular projects are encouraged to contact the responsible agency. Comments may be provided at a public meeting to be held June 25, 2003 in Bethesda Maryland (2) or submitted in writing to the pertinent agency or to: Ms. Vickie Garrett, Antimicrobial Resistance, Office of the Director, NCID, CDC, Mail stop C-12, 1600 Clifton Road, NE, Atlanta, GA 30333; telephone 404-639-2603; fax 404-639-4197; or e-mail aractionplan@cdc.gov.

SURVEILLANCE

The surveillance of drug-resistant infections requires coordination of activities by national, regional, state, and local organizations and the accurate detection of AR by clinical and public health laboratories. Because antimicrobial drug use influences the incidence and prevalence of resistance, surveillance for the extent and type of antimicrobial drug use is also needed. A national plan for surveillance of AR must include providing support to states to ensure that local needs for surveillance are met (including clinical laboratory proficiency), that surveillance is conducted for resistant organisms with a significant burden of disease or that pose especially dangerous threats to health, and that new tools are developed for detecting emerging resistance. A national plan must allow different approaches to surveillance of various organisms since it is unlikely that a single, nationwide methodology would be suitable for all pathogens in all settings, or would provide flexibility to meet local needs. However, standards and methods are being promoted that will allow comparison of data among various geographic areas and for national estimates of resistance for certain organisms.

Top Priority Action Items in this focus area include the following:

- With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities and the roles of clinical, reference, public health, and veterinary laboratories. The plan should be consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed. (Action Item #2)

- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, agriculture, veterinary medicine, and consumer products. (Action Item #5)

NATIONAL SURVEILLANCE PLAN

National surveillance of AR in microorganisms that pose a threat to public health is being developed and implemented by coordinating existing projects and addressing unmet needs in collaboration with partners. Standards and methods such as the National Electronic Diseases Surveillance System (NEDSS) are being promoted in healthcare settings, large national laboratory companies, and in public health reporting by state health departments. In addition, when focused surveillance for critical pathogens is conducted, methods are being developed that can be used by state health departments and healthcare facilities not currently involved in federally-sponsored systems. Notable examples include surveillance methods for: drug resistant *Streptococcus pneumoniae* (DRSP), for which a manual is in development and a national meeting was held with state and other partners; community-associated Methicillin resistant *Staphylococcus aureus* (MRSA), for which various methods are being examined including population-based surveillance (e.g., Active Bacterial Core Surveillance project, the National Health and Nutrition Examination Surveys [NHANES]) and a national meeting was held with state and other partners; and healthcare-associated infections, for which CDC is developing the National Healthcare Safety Network (NHSN), an internet-based nationwide network that will

enhance the ability to monitor and track trends of usage and resistance of microbes to antimicrobial agents in a variety of healthcare delivery settings.

When surveillance methods have not been well established, smaller scale surveillance is being evaluated to determine appropriate standards, methods, and utility of the data. For example, for HIV resistance, CDC completed the Sentinel Surveillance of Variant and Resistant Strains of HIV project in ten cities, is beginning the Pilot Antiretroviral Drug Resistance Testing (ARVDRT) Project in four states, and beginning resistance testing among persons newly diagnosed with HIV in 26 states. A national meeting was sponsored by CDC in 2003 to discuss these projects and other issues related to antiretroviral resistance surveillance and testing.

For some organisms, available laboratory tests are not optimal to detect resistance (e.g., Chlamydia, trichomonas, lice). For these organisms, research is helping to develop methods of detection, and in turn, tools to conduct surveillance. For rare patterns of resistance in common pathogens of which widespread dissemination would be a major health threat (e.g., vancomycin-tolerant and vancomycin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *S. aureus* [VRSA]) sentinel or pilot surveillance is being conducted to ensure timely and accurate detection of these infections. In 2002, the Surveillance for Emerging Antimicrobial Resistance Connected to Healthcare (SEARCH) project detected two infections with VRSA. (5)

Well-established, national surveillance for drug-resistant *Mycobacterium tuberculosis* continues. This program clearly specifies activities that may be conducted at national, state, and local levels.

Standardized methods are being promoted by CDC to ensure comparability of results among geographical and institutional systems (e.g., NEDSS, cumulative antimicrobial susceptibility data). Public health officials, clinicians, and researchers are involved with many of the surveillance programs and provide for timely dissemination of data to interested parties. Necessary core capacities at state and local levels are being supported through grants (e.g., Epidemiology and Laboratory Capacity Cooperative Agreement). National AR surveillance has been built upon existing disease surveillance infrastructure. Methods and standards from current projects are either being expanded to encompass greater geographic areas or are being modified so they can be exported to areas that are not currently conducting surveillance. This is particularly true in the areas of healthcare associated infections, surveillance for *Streptococcus pneumoniae* infections, and surveillance for AR among foodborne pathogens and infections. Surveillance is also being conducted where possible through microbiology laboratories in large healthcare networks (e.g., VA Emerging Pathogens Initiative, DoD AR Surveillance Network).

Improved surveillance for AR in agricultural settings will allow early detection of resistance trends in pathogens that pose a risk to animal and plant health, as well as in bacteria that enter the food supply. This task is being accomplished in various ways, e.g., the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria has been expanded to all 50 states and has launched a study of antimicrobial resistant pathogens found on retail foods. NARMS is a collaboration among CDC, U.S. Food and Drug Administration (Center for Veterinary

Medicine) and U.S. Department of Agriculture (Food Safety and Inspection Service and Agricultural Research Services).

Surveillance data will also help improve understanding of the relationship between antimicrobial drugs and pesticides used on plants and the emergence of drug resistance. The first steps in this regard for antimicrobial pesticide products are being taken by EPA, which is reviewing current scientific data on whether use of antimicrobial pesticide products results in the development of resistance to either the pesticide products themselves or to human or animal drugs.

Available, reliable drug susceptibility data are essential for accurate AR surveillance. Examples of activities to improve accuracy of AR detection and reporting include training and proficiency testing programs for diagnostic laboratories. CDC now has a Web site (M.A.S.T.E.R) (http://www.phppo.cdc.gov/dls/master/default.asp) which provides up-to-date information and advice on antimicrobial susceptibility testing issues in clinical microbiology laboratory practice. CDC, in collaboration with the Association of Public Health Laboratories, has published a CD-ROM that provides materials necessary for training laboratory workers to test bacterial isolates for resistance to antimicrobial agents and issue accurate reports to physicians (http://www.aphl.org/ast.cfm). CDC continues to train laboratorians through the National Laboratory Training Network. CDC is promoting and further refining standardized methods for detecting drug resistance in important pathogens, including programs for *Chlamydia*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, HIV and influenza. In 2002, CDC's Applied Research on Antimicrobial Resistance grant program funded projects to validate or develop breakpoints to define resistance among certain human pathogens of public health importance. Public and private sector partners have started to address barriers to AR testing and reporting, e.g., barriers due to changes in healthcare delivery.

As in the past, all surveillance activities are being conducted with respect for patient and institutional confidentiality.

MONITORING ANTIMICROBIAL DRUG USE

Methods for monitoring patterns of antimicrobial drug use are being developed and implemented as a component of the national AR surveillance plan. This information is essential for interpreting trends and variations in rates of AR, improving our understanding of the relationship between drug use and resistance, identifying and anticipating gaps in availability of existing drugs, and identifying interventions to prevent and control AR. CDC supports projects that collect data through new and existing healthcare data systems, through surveys of outpatient physicians, and through other databases (e.g., marketing surveys). The enhanced collection and electronic transfer of data on Antimicrobial Use and Resistance (AUR) component of the National Nosocomial Infections Surveillance (NNIS) allows participating hospitals to collect data that provide a national estimate of the amounts of antimicrobial agents used in these hospitals. Under the NHSN's Medication-Associated Adverse Event Module, an initial focus will be on establishing electronic reporting of antimicrobial use data. Analysis of antimicrobial use databases has proven to be complex, requiring sophisticated statistical methods and linkage

with appropriate clinical information and with databases on resistant infections to be most useful. This is being done for the healthcare and community settings.

PREVENTION AND CONTROL

The prevention and control of drug-resistant infections requires measures to promote the appropriate use of antimicrobial drugs and prevent the transmission of infections (whether drug-resistant or not). Top Priority Action Items in this focus area include the following:

- Conduct a national public health education campaign to promote appropriate antimicrobial drug use as a national health priority. (Action Item #25)

- Develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing. (Action Item #26)

- Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for healthcare and extended care settings and in the community. Promote adherence to practices proven to be effective. (Action Item #39)

- In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs. (Action Item #58)

- Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale. (Action Item #63)

APPROPRIATE DRUG USE

Appropriate drug-use policies are being promoted in programs targeting both the public and clinicians. AHRQ, through its network of Centers for Education and Research on Therapeutics, has sponsored education and research projects to evaluate and improve antimicrobial drug use, e.g., shared decision-making and inappropriate antibiotic use, a diagnostic decision aid for pediatric sinusitis, reducing antimicrobial prophylaxis errors, and the use of antimicrobials in acute otitis media. CDC expanded its National Campaign for Appropriate Antibiotic Use in the Community by increasing (to 26 in 2002) the number of state health departments funded to develop state-based coalitions of partners. CDC also worked with partners (e.g., the Coalition for Affordable Quality Healthcare) to develop intervention programs for healthcare delivery organizations, developed a medical curriculum, and extended a previous focus on pediatric prescribing to adults through development of prescribing principles for upper respiratory

infections and patient education materials. With the National Committee for Quality Assurance, CDC proposed two Health Plan Employer Data and Information Set (HEDIS®) performance measures for children -- Pharyngitis and upper respiratory infections. These measures were adopted May 2003. The DoD is developing an intervention program to enhance the communication skills of primary care providers on the prudent use of antimicrobial agents in DoD settings. The VA has introduced guidelines and training programs regarding appropriate antimicrobial drug use for staff and trainees in its large network of healthcare facilities. The success of programs to improve use in outpatients has been demonstrated by encouraging data from the National Ambulatory Medical Care Survey, which indicate that antibiotic prescribing rates for children seen in physician offices have declined in recent years (3).

To improve prescribing in healthcare settings, CDC launched the national campaign *Prevent Antimicrobial Resistance* in March 2002, initially focusing on hospital care of adults. This campaign involves working with partners to emphasize 12 evidence-based steps for diagnosis of infection, appropriate treatment, appropriate use of antibiotics, and prevention of infection transmission. After its initial launch, a variation of the 12-step campaign was developed for dialysis patients. Additionally, several health commuication tools were developed and disseminated to various health systems including brochures, slide sets, posters, pockets cards, and badge cards. CDC also worked with the National Committee for Clinical Laboratory Standards to develop guidelines for clinical microbiology laboratories on how to compile and report summaries of cumulative antimicrobial susceptibility data in a standardized manner to aid in clinical decisions. CMS is using the Medicare quality improvement organizations in all 50 states to promote optimal antibiotic use for inpatient pneumonia treatment and surgical infection prevention. A CMS Web-based decision support system targets improved antibiotic therapy in rural hospitals. CMS is also developing interventions to improve the use of antibiotics in long-term care facilities and physicians' offices. FDA has approved a new labeling rule intended to educate physicians and the public about the resistance problem and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary. The Final Labeling Rule was published in the Federal Register on February 6, 2003, and the rule will go into effect February 6, 2004.

PREVENTING INFECTION TRANSMISSION

Widespread use of a new pneumococcal vaccine for children was temporally associated with unprecedented declines in cases of invasive pneumococcal disease and in the proportion of cases resistant to antimicrobial drugs. CDC data from ongoing population-based surveillance of invasive pneumococcal disease in 7 geographic areas indicate that the number of cases in children under 2 years of age declined by 69% in 2001 (compared with data from 1998 and 1999). The number of cases of invasive disease in adults also declined, suggesting that vaccine use may have helped to decrease transmission of pneumococci to unvaccinated persons. Five of the seven-pneumococcal serotypes in the vaccine account for most of the pneumococcal strains that are resistant to penicillin and other antibiotics. The rate of disease caused by strains that were not susceptible to penicillin was 35% lower in 2001 than 1999 (Reference #).). CDC contracts for 52% of the national market share for pediatric vaccines and provides funds and technical assistance to 64 state, territorial, and local health departments for immunization programs. CMS promotes and pays for pneumococcal and influenza vaccination of Medicare beneficiaries. CMS's ongoing Healthy People 2010 has a goal of increasing targeted adult

immunization rates to 90%. The campaign is funded and focused on improving immunization rates among minorities and other vulnerable populations.

The effectiveness of current and novel infection control practices is being evaluated in CDC's network of Centers of Excellence in Healthcare Epidemiology, a program in which prevention research to improve infection control practices is conducted at 7 academic medical centers. Infection control is also a major element of the campaign *Prevent Antimicrobial Resistance*, outlined above, and of the comprehensive demonstration programs outlined below. VA has an ongoing program to evaluate the outcome of infection control interventions for serious infectious diseases. Improved infection control practices reduce the spread of infections in healthcare settings and thus also decrease the use antimicrobial drugs.

FDA REGULATORY FRAMEWORK FOR ANTIMICROBIAL DRUGS IN FOOD ANIMAL PRODUCTION

A regulatory framework for antimicrobial drugs used in food-animal production, proposed by FDA, was discussed extensively with stakeholders, and the concepts were refined on the basis of comments received. A draft guidance document for industry incorporating these changes was published in September 2002 and a public meeting held October 2, 2002 to explain the guidance and solicit additional comments. An approach for evaluation of drugs according to their importance in human medicine has been incorporated into the pre-approval assessment strategy and is fully explained in the draft guidance document. That portion of the document was taken to a FDA Anti-Infective Drugs Advisory Committee in January 2003. Comments from the advisory committee as well as comments received at the public meeting in October and all written comments have been evaluated. Changes are being incorporated into the document and a final guidance implementing the regulatory framework is expected to publish later in 2003. An analysis (risk assessment) of the relationship between the emergence of quinupristin-dalfopristin resistant *Enterococcus faecium* in humans and the use of virginiamycin in food animals is in progress. A risk assessment of the use of fluoroquinolones in poultry was completed; given its conclusions, FDA proposed withdrawing approval of fluoroquinolones for use in poultry. One of the two affected drug manufacturers withdrew its fluoroquinolone product, and the other requested a hearing which is in progress. These FDA actions address the need for antimicrobial drug use in agriculture and veterinary medicine, while ensuring that such use does not pose a risk to human health.

COMPREHENSIVE DEMONSTRATION PROJECTS

Comprehensive demonstration projects involving a wide variety of nonfederal partners were implemented to prevent and control AR through multiple interventions (e.g., surveillance, appropriate drug use, optimized diagnostic testing, immunization practices, and infection control). CDC-sponsored projects included a regional approach involving a coalition of healthcare facilities and business and community leaders in Pittsburgh, a statewide program in Wisconsin, a group of healthcare institutions in Chicago, and an integrated approach in rural communities in Utah and Idaho. The success of comprehensive regional approaches such as these is illustrated by the control of vancomycin-resistant enterococci in the Sioux City, Iowa area, with leadership from the Sioux City Health Department and support from the Iowa, South Dakota, and Nebraska State Health Departments, and CDC. (4)

RESEARCH

Knowledge and understanding of the growing problem of antimicrobial resistance (AR) is a prerequisite for a planned and coordinated federal response to this challenge. Numerous federal agencies are engaged in developing the scientific base of knowledge through support and conduct of bench, applied, and clinical research. The NIH has the lead in this area, but increasingly the federal agencies are collaborating and pooling resources to accomplish the action items within this chapter. Research accomplishments in the following areas will be highlighted in this executive summary:

- Supporting additional research, including high risk and high payoff research in nontraditional fields that will lead to an increased understanding broadly of: microbial physiology, ecology, genetics, mechanisms of resistance, host factors; and the impact of variable antimicrobial use patterns, preventive, therapeutic, and growth promoting agents, and environmental residues on the emergence and spread of resistant organisms and resistance factors. (Action Item #67)

- Providing to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens. (Action Item #70)

- Encouraging basic and clinical research in support of novel approaches to preventing or treating infections with resistant organisms that occur in humans and animals by partnering with academia and the private sector. (Action Item #77)

EXPANDING THE RESEARCH BASE

Over the past year a number of new initiatives have extended grant and funding opportunities related to or including antimicrobial resistance, to new groups and investigators, and are serving to stimulate this research area. These initiatives include basic, applied, and product-oriented research areas and have been directed at academicians and industrial researchers. The NIH announced and made awards through the "Innovative Approaches to Combat Antimicrobial Resistance" initiative to stimulate novel research including high risk and high payoff studies in nontraditional fields, with a goal of acquiring a better understanding of the factors affecting the development of resistant pathogens and spread of resistance genes in order to direct actions to diagnose, control, and treat AR. The "Partnerships for Novel Therapeutic, Diagnostic and Vector Control Strategies in Infectious Diseases" initiative supported the development of drugs and diagnostics for diseases of public health importance including infections for which drug resistance is making current therapies ineffective. A key component of this initiative is the development of appropriate partnerships among government, academia, and the biotechnology, chemical and pharmaceutical industries, as an attempt to stimulate industry participation in these research areas. Other broad initiatives, such as the Small Research Grant and the Exploratory/Developmental Research Grant announcements accept investigator initiated studies,

including AR applications, with a goal of bringing new investigators into the field and infusing new ideas, techniques, and points of view into the scientific area.

SCIENCE AND TECHNOLOGY SUPPORT

The NIH and other federal agencies have made a significant investment in the sequencing of whole pathogen genomes. Coordination of these numerous activities across federal agencies occurs through the Microbe Project consortium including NIH, USDA, FDA, and EPA. The ultimate goal is to foster the burgeoning field of pathogen genomics which, supported by the development of various new technologies, continues to uncover clues to microbial functioning that hold promise for the prediction of disease progression and for patient care and treatment, ultimately translating genomic information into clinical applications. Over the past year NIH's Pathogen Functional Genomic Resource Center has provided microarray slides, relational databases, computational tools, and training to researchers to study three organisms that pose important public health challenges: *Staphylococcus aureus, Salmonella typhimurium,* and *Streptococcus pneumoniae.* These activities have accelerated our understanding of the genetic basis of antimicrobial resistance in these and other pathogens. The functional analysis of genes and proteins in whole organisms and cells being carried out through federally supported research projects, combined with the availability of the human genome, advances our understanding of host pathogen interactions and affords opportunities to impact disease causing processes.

New levels of collaboration were forged in addressing the emerging challenge of vancomycin resistant *S. aureus* and the phenomenon of community-associated methicillin resistance in *S. aureus*. NIH's Network on Antimicrobial Resistance in *Staphylococcus Aureus* was established as a network of basic researchers and clinical investigators studying resistance in this important hospital and community pathogen. Expansion of the bacterial repository, including inclusion of recently identified staphylococcal isolates that are resistant to vancomycin, has been made possible through the efforts of the Centers for Disease Control. Discussions are underway for collaborative research studies utilizing the repository isolates and involving academic, government and industry participants.

NOVEL THERAPEUTIC AND PREVENTIVE APPROACHES

Research partnerships are advancing the development and testing of novel products to address resistant pathogens. Tuberculosis has a major impact on health through out the world, with the emergence of resistance seriously complicating therapy. The Global Alliance for TB Drug Development, with CDC, NIH and USAID as partners and over 30 stakeholder organizations involved, is stimulating new drug development for TB. Over the last year a process for soliciting and funding drug discovery and development proposals was established with 11 awards made and promising compounds under development. Other potential compounds with promise as TB drugs are being screened through a variety of NIH contracts and collaborations. The search for new antimicrobials in unusual settings is being carried out through the International Cooperative Biodiversity Groups Program in collaboration with the NIH, the National Science Foundation and the USDA. Six awards have been made to multidisciplinary research groups that also include in-country researchers, to explore natural products as a source of pharmaceuticals. Through these activities and others described in the Task Force Inventory of Projects, NIH and

the other federal partners are investing in target discovery and moving promising products down the developmental pathway.

PRODUCT DEVELOPMENT

New products must keep pace with the development of pathogens resistant to currently available antimicrobials. We need to foster the development of new classes of antimicrobial agents that are effective against resistant organisms. We also need to develop vaccines and anti-infective devices with the potential to prevent infections. In addition, the development of improved diagnostic tools is needed to aid in the appropriate use of therapeutic agents.

Product development is also an important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to encourage the development and use of veterinary drugs and agricultural practices that are unlikely to stimulate resistance to important human drugs or spread resistant pathogens to humans. In addition, we need to focus attention on developing strategies to prevent animal infections (e.g., vaccines, changes in husbandry).

Pertinent issues include:

- Researchers and manufacturers need to be better informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics and of potential markets for these products.

- Market incentives and regulatory processes need to be adequate to stimulate the development of AR products while promoting the appropriate use of new and currently available agents.

- The development and use of antimicrobial drugs and related products in agriculture and veterinary medicine need to be optimized to reduce the development and transfer of resistance to pathogens that can infect animals and humans.

Top priority action items in this focus area include:

- Use the existing mechanisms of FDA advisory committees and workshops to identify and publicize priority public health needs in human and animal medicine for new AR products. (Action Item #79)

- Identify ways to promote the development and/or appropriate use of AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate. (Action Item #80)

ASSESSMENT OF FUTURE NEEDS FOR AR PRODUCTS

To provide a systematic assessment of the current status and projected future needs for AR products, a cooperative interagency effort involving stakeholders including regulated industry is

intended to identify and publicize priority public health needs in human and animal medicine for new AR products. FDA has chosen to perform these cooperative activities within an existing framework (i.e., pre-existing advisory committees) and co-sponsored workshops with other stakeholders to enhance the efficiency and the applicability of the results of such discussions. FDA has begun this process through the following ongoing activities:

- Determine which resistant pathogens are of the greatest public health importance in terms of multidrug resistance and for which there are few available therapies.

- Identify current areas/anticipate future areas of greatest need for drug development.

- Consider and assess proposed resistant pathogen claims for product labeling

- Address clinical design issues in acute otitis media, acute bacterial sinusitis, and acute exacerbations of chronic bronchitis, and other indications in attempts to streamline drug development through higher quality data.

- Consider the perspectives of experts from a range of disciplines on issues such as modeling future resistance trends, identifying product needs and potential markets, considering appropriate AR surveillance data and numbers of patients at high risk of developing drug resistant infections.

- Address issues of incentives and disincentives for developing AR products.

- Reassess AR product priorities regularly.

- Evaluate the availability of currently approved, critical products for drug resistant infections when shortages or the potential for shortages exists and develop strategies to ensure that the supply of these products meet public health needs.

- Coordinate information and priorities developed through cooperative efforts with other agencies and stakeholders to further advance action efforts in research, prevention and control, and product development.

- Consider government's role in the discovery of drugs and other products targeted to address areas in which market incentives are limited and unmet needs exist. This role could use intramural, extramural or partnership-type mechanisms. The products developed under such mechanisms could be licensed commercially either with or without specific stipulations about use.

PROMOTING DEVELOPMENT OF AR PRODUCTS

FDA is developing guidance on the development of antimicrobial drugs for diseases due to infections with resistant pathogens. FDA has held meetings with industry stakeholders, and made presentations at numerous scientific and public advisory committee meetings. FDA is also developing guidance documents to promote the development of novel types of AR products (e.g.,

topical antimicrobicides, plant-based vaccines). Finally, FDA is considering additional incentives beyond existing regulatory tools to further stimulate AR drug development. Future plans include:

- Consult with outside stakeholders to explore potential pilot programs that may stimulate antimicrobial drug development.
- Consult with other government agencies on programs that may encourage antimicrobial drug development

REFERENCES

1. Available at http://www/cdc/gov/drugresistance/actionplan/index.htm

2. Linda F. McCaig, Richard E. Besser, and James M. Hughes. Trends in Antimicrobial Prescribing Rates for Children and Adolescents JAMA 2002 287: 3096-3102.

3. Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin-resistant enterococcus in health care facilities in a region. N Engl J Med. 2001; 344:1427-33.

4. Whitney C. G., Farley M. M., Hadler J., et al. Decline in Invasive Pneumococcal Disease after the Introduction of Protein–Polysaccharide Conjugate Vaccine N Engl J Med 2003; 348:1737-1746, May 1, 2003.

5. Chang S., Sievert D. M., Hageman J. C., et al. Brief Report: Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the vanA Resistance Gene. N Engl J Med 2003; 348:1342-1347, Apr 3, 2003.